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Allogeneic Marrow Transplantation for Myeloproliferative Disorders Other Than Chronic Myelogenous Leukemia: Review of Forty Cases

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The role of allogeneic marrow transplantation as treatment of myeloproliferative disorders other than chronic myelogenous leukemia is not yet determined. At our center, 1 patient with primary myelofibrosis, 1 with mastocytosis, and 4 with myeloid metaplasia have been transplanted using HLA-identical sibling donors. All patients engrafted with full donor chimerism, and morphologic and cytogenetic manifestations of disease in the marrow resolved posttransplant. Three patients died; two with relapse and one from infection. The other three patients are alive in remission at 24+, 28+, and 32+ months posttransplant. Including these cases, a total of 40 patients transplanted for myeloproliferative disorders have been reported. The most common indications for transplantation were cytopenias, increasing blasts in marrow or blood, uncontrolled counts on conventional therapy, poor prognosis cytogenetics, organ dysfunction, and consolidation after induction therapy for blast transformation. Using the outcome data published for these patients, the actuarial estimate of 3-year survival is 55% (95% C.I., 44–76%) with a median reported follow-up of survivors of 21 months (range, 4–158 months). For patients with myeloproliferative disorders and evidence of accelerated disease, HLA-identical marrow transplantation is well tolerated and can result in an extended disease-free survival. Am. J. Hematol. 57:24–28, 1998.

Key words: allogeneic bone marrow transplantation; myeloproliferative disorders; myelofibrosis; myeloid metaplasia; hypereosinophil syndrome; polycythemia vera

INTRODUCTION

Extensive experience has established the use of allogeneic marrow transplantation for treatment of chronic myelogenous leukemia [1], yet its role in the treatment of other myeloproliferative disorders is unclear. Many of the myeloproliferative disorders have a long natural history, and the indications for transplantation have not been identified. Numerous cases have been reported suggesting the benefit of allogeneic transplantation for patients with advancing disease [2–28], but controversies remain regarding the impact of marrow fibrosis and hypersplenism on engraftment. Herein we present six patients transplanted for myeloproliferative disorders and provide a critical review of the literature to address the controversial issues.

PATIENTS AND METHODS

From 1988 through 1994, six adults with HLA-matched related donors underwent allogeneic transplantation at the University of Texas M.D. Anderson Cancer Center as treatment for myeloproliferative disorders other than chronic myelogenous leukemia (Table I). The diagnosis of chronic myeloproliferative disorder was made on the basis of the history, typical manifestations in the peripheral blood and marrow (lineage hyperplasia or panleukocytosis similar to chronic myelogenous leukemia and without excess blasts, or myelofibrosis without other etiology), the absence of a Philadelphia chromosome on cytogenetic analysis, and the absence of a rearrangement of the bcr gene. Conventional management prior to transplantation was conducted by the referring physician. For transplantation, the patients were treated on protocols approved by the Institutional Review Board, and written informed consent was obtained from each patient.

Snook's reticulin stain (ammoniacal silver procedure)

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TABLE I. Patient Characteristics at Transplantation*

	Patient number					
	1	2	3	4	5	6
Age (years)/sex	34/Female	32/Male	49/Male	39/Female	51/Male	40/Male
Diagnosis	Primary myelofibrosis	Mastocytosis	Myeloid metaplasia	Myeloid metaplasia	Myeloid metaplasia	Myeloid metaplasia
Interval to BMT (months)	22	9	41	10	4	5
Splenomegaly	No	Yes	(Spenectomy)	No	Yes	Yes
Marrow fibrosis	Grade 4	No	Grade 4	No	Grade 1	Focal[a]
Marrow blasts (%)	1.0	5.0	1.0	N.D.	1.0	0.5
Peripheral blood	Left-shifted with 11% blasts	Left-shifted with 21% monocytes and 20% eosinophils	Left-shifted with 17% monocytes and 15% eosinophils	Left-shifted with 21% blasts	Left-shifted with 20% eosinophils	Normal differential
Leukocytes ($\times 10^9$/L)	3,600	15,600	15,100	16,300	5,800	2,700
Neutrophils ($\times 10^9$/L)	1,944	6,552	4,077	8,313	2,552	1,755
Hemoglobin (g/dL)	8.8	7.1	11.6	9.1	10.0	7.5
Platelets ($\times 10^9$/L)	10,000	44,000	396,000	312,000	245,000	183,000
Cytogenetics	46,XX	46,XY	46,XY,t(8;9)	47,XX,+8	47,XX,+8	46,XY,t(7;10)
Prior therapy	Filgrastim	HU, PRED	HU, VCR/PRED	IFN/HU	HU	IFN/HU
BMT indication	> 5% blasts, cytopenias	Mastocytosis, cytopenias	Consolidation	> 5% Blasts, +8	+8, persistent splenomegaly	Persistent splenomegaly

[a]Slide not available for review. Originally reported as focal fibrosis.
*N.D., not done; HU, hydroxyurea; PRED, prednisone; VCR, vincristine; IFN, interferon.

was performed on marrow biopsy samples to assess fibrosis. Biopsies were graded 1–4 depending on the amount of reticulin seen in areas showing no hemorrhage or artefactual depletion of cells. Grade 1 had less than 25% involvement; grade 2 had 25–50% involvement; grade 3 had 50–75% involvement; and grade 4 had more than 75% involvement.

The preparative regimens, described previously, included thiotepa, busulfan, and cyclophosphamide [29], etoposide, cyclophosphamide and total-body irradiation [30], and piperazinedione and total-body irradiation [31]. Graft-vs.-host disease (GVHD) prophylaxis consisted of tacrolimus or cyclosporine with methotrexate or methylprednisolone [29–31]. The details of marrow or blood stem cell collection and posttransplant supportive care have been published [29–31]. None of the marrows was T-cell-depleted.

Patient outcome (Table II) was assessed by standard criteria. Neutrophil recovery was defined as the first of 3 consecutive days that the absolute neutrophil count exceeded 1.0×10^9/L, and platelet recovery was defined as the day that the platelet count exceeded 50×10^9/L with no platelet transfusions the following week. Normalization of the blood counts was defined as an absolute neutrophil at least 2.5×10^9/L, hemoglobin at least 10 gm/dL, and platelet count at least 150×10^9/L without transfusions. Marrow biopsies and aspirates were examined at 1, 3, 6, 12, 18, and 24 months after transplantation. Hematopoietic chimerism was evaluated by restriction fragment length polymorphisms (RFLP). GVHD was diagnosed and graded according to the consensus criteria [32].

RESULTS

Patient 1 developed progressive pancytopenia and extensive marrow fibrosis just following primary treatment for Hodgkin's disease. No evidence of marrow involvement by Hodgkin's disease was seen. At the time of transplantation 2 years later, she was transfusion-dependent with increasing blasts in the peripheral blood and dense marrow fibrosis. Her posttransplant course was significant for pulmonary hemorrhage requiring hypertransfusion of platelets, but neutrophil recovery was timely. Resolution of marrow fibrosis was documented with serial biopsies, and the blood counts normalized at 8 months posttransplant. Low-risk, clinical extensive chronic GVHD occurred at 9 months posttransplant and responded to treatment with methylprednisolone. At 2 years, the marrow biopsy had 20% cellularity with trilineage engraftment and no fibrosis. Cytogenetic and RFLP analysis demonstrated complete donor chimerism.

Patient 2 had systemic mastocytosis with an associated myeloproliferative disorder. He presented with fevers, night sweats, fatigue, anemia, and a deep vein thrombosis. The marrow biopsy was hypercellular and showed perivascular and paratrabecular nodules of mast cells involving approximately 30% of the biopsy. Before transplantation, he was transfusion-dependent with an absolute monocytosis and eosinophilia despite conventional treatment. Engraftment posttransplant was rapid. The

TABLE II. Transplant Outcome*

	Patient number					
	1	2	3	4	5	6
Preparative regimen	Thio/Bu/Cyc	Thio/Bu/Cyc	Thio/Bu/Cyc	VP/Cyc/TBI	VP/Cyc/TBI	Pip/TBI
Transplant	Marrow	Blood stem cells	Marrow	Marrow	Marrow	Marrow
GVHD prophylaxis	FK506/MTX	CSA/MP	CSA/MTX	CSA/MTX	CSA/MTX	CSA/MTX
Neutrophils > 1×10^9/L	Day 18	Day 11	Day 13	Day 21	Day 20	Day 26
Platelet > 50×10^9/L	Day 87	Day 60	Day 16	Day 20	Day 38	Day 31
Normal blood counts	Day 253	Day 128	Day 27	Day 42	Day 120	Day 95
Grades 2–4 GVHD	No	No	No	No	No	Yes
Chronic GVHD	Yes	No	No	No	No	No
Outcome	Alive, 32+ months	Alive, 24+ months	Alive, 28+ months	Relapse, 8 months Expired, 28 months	Relapse, 8 months Expired, 17 months	Expired, 6 months Infection

*Thio, thiotepa; Bu, busulfan; Cyc, cyclophosphamide; VP, etoposide; TBI, total-body irradiation; Pip, piperazinedione; FK506, tacrolimus; MTX, methotrexate; CSA, cyclosporine.

mast cells were absent from the marrow by 1 month posttransplant, and the blood counts normalized by 4 months. Splenomegaly resolved, and a marrow biopsy at 2 years had 25% cellularity, trilineage engraftment, and no mast cells.

Patient 3 had progressive cytopenias, a hypercellular fibrotic marrow and splenomegaly. His course was typical of the 8p myeloproliferative syndrome [28]. Splenectomy was performed for hypersplenism. He was treated with vincristine and prednisone for lymphoid blast transformation of myeloid metaplasia, and presented for transplantation as consolidation. Engraftment was prompt with normalization of the blood counts at 1 month posttransplant. At 2 years, no abnormalities were seen in the marrow, RFLP analysis showed complete donor chimerism, and cytogenetics were 46,XY.

Patient 4 was referred for transplantation with trisomy 8 and increasing blasts in the blood after 8 months of treatment with interferon and hydroxyurea for panmyelosis. Hematopoietic recovery posttransplant occurred without problems. There was complete donor engraftment, and no evidence of trisomy 8 in the marrow posttransplant. The blood counts normalized by 6 weeks. Steroids were given for bullous pemphigoid at 4 months. At 8 months, blasts in the marrow and blood increased, and cytogenetics showed a t(1;6). She subsequently expired during conventional treatment of recurrent overt blast transformation.

Patient 5 with myeloid metaplasia had persistent splenomegaly, trisomy 8, marrow fibrosis, and increasing eosinophilia while being treated with hydroxyurea. The posttransplant course was uncomplicated. Donor engraftment was complete, and the trisomy 8 and marrow fibrosis were eliminated at 1 month. Unfortunately, blasts in the blood and marrow increased at 8 months, and the patient expired in relapse 17 months posttransplant.

Patient 6 with myeloid metaplasia achieved a hematologic response with interferon and hydroxyurea but had persistent splenomegaly, marrow fibrosis, and t(7;10) on cytogenetic analysis at the time of transplantation. Hematopoietic recovery posttransplant occurred as expected with trilineage engraftment and no fibrosis in the marrow. Cytogenetic analysis posttransplant documented complete donor engraftment and no evidence of the t(7;10). Grade 2 GVHD of the skin responded to treatment with methylprednisolone. At 4 months posttransplant, he developed hematuria due to cytomegalovirus resistant to treatment with ganciclovir. He expired 6 months posttransplant with hemorrhagic cystitis and atypical mycobacteria pneumonia.

DISCUSSION

In our series of patients transplanted for myeloproliferative syndromes, all engrafted promptly with normalization of the marrow morphology, and three of the six patients are alive and free of disease more than 2 years after transplantation. While this report confirms that allogeneic marrow transplantation can be used effectively for treatment of chronic myeloproliferative disorders other than chronic myelogenous leukemia, the limits of this approach need to be defined.

We conducted a MEDLINE search over a 30-year period for all reports of HLA-identical allogeneic marrow transplantation for myelofibrosis, myeloid metaplasia, hypereosinophil syndrome, mastocytosis, polycythemia vera, or essential thrombocythemia. Patients with a Philadelphia chromosome or a bcr gene rearrangement and those who fulfilled the criteria for acute megakaryoblastic leukemia were not included. An additional 34 cases were identified that had adequate information to confirm the diagnosis and evaluate the outcome [2–29]. The clinical characteristics of all 40 patients are summarized in Table III.

Median survival of 5–10 years is expected overall for patients with myeloproliferative disorders, but the outcome of individual patients varies from months to de-

TABLE III. Summary of Published Cases of HLA-Identical Allogeneic Marrow Transplantation for Myeloproliferative Disorders (From References [2–29] and Current Report)

Number of patients	40[a]
Median age (range)	30 yrs (3–51)
Sex	
Male	24
Female	16
Diagnosis	
Myelofibrosis	24
Myeloid metaplasia	6
Hypereosinophil syndrome	6
Mastocytosis	2
Polycythemia vera	2
Indication for transplantation[b]	
Cytopenias	24
> 5% marrow blasts	9
Rising blood counts on therapy	7
Poor prognosis cytogenetics	6
Organ infiltration	5
Consolidation	2
Not stated	1
Splenectomy	8/33
Preparative regimen	
TBI-based	30
Busulfan-based	10
Transplant	
Marrow	38
Blood stem cells	2
Engrafted	34/36
Grades 2–4 GVHD	15/34
3-Year survival (95% C.I.)	55% (44–76%)
Deaths	
Infection	6
GVHD ± infection	2
Veno-occlusive disease	2
Relapse	4

[a]Number of patients or Number of patients/number evaluable unless indicated otherwise.
[b]Some patients had more than one indication listed, so the sum of the numbers exceeds 40.

cades. Staging systems have been devised for myeloid metaplasia and primary myelofibrosis that identify subpopulations with median survivals as low as 1–2 years, groups for which the risk-benefit ratio might favor transplantation [33,34]. Poor prognostic features with conventional therapy included anemia, leukopenia, uncontrolled leukocytosis, and systemic symptoms. Cytogenetic abnormalities were also predictive of leukemic transformation [34]. In the literature series (Table III), these characteristics, in addition to extramedullary disease, were cited as indications for transplantation. The overall actuarial reported survival of the patients with chronic myeloproliferative disorders plateaus at 55% with a median follow-up of 21 months (range, 4–158 months) for survivors (Table III). This suggests that there may be a survival benefit using transplantation for patients with high-risk features that parallel the criteria for accelerated phase of chronic myelogenous leukemia.

Neutrophil recovery was not delayed in our one patient with primary myelofibrosis. In fact, our two patients with grade 4 fibrosis are long-term survivors. Concern regarding the ability of transplanted marrow to engraft in a densely fibrotic marrow space was raised initially by Rajantie et al. [6] who reported that engraftment was delayed and the risk of graft failure higher in patients with fibrotic marrow, and this was supported by a single case from Creemers et al. [17]. However, 22 patients with primary myelofibrosis have reportedly achieved neutrophil recovery after allogeneic marrow transplantation [2,3,5,7,8,10–14,16,19,21,25], and in a case-control study, Soll et al. [35] failed to confirm that marrow fibrosis is a significant impediment to engraftment. Thus, marrow fibrosis should not be considered a contraindication to transplantation.

Schmitz et al. [19] advocated the use of splenectomy pretransplant for patients with myelofibrosis and splenomegaly in order to promote engraftment. Of the 8 reported cases of splenectomy in patients transplanted for myeloproliferative syndromes, only two were for hypersplenism and poor engraftment [18,19]. All three of our patients with splenomegaly had complete normalization of the blood counts within 4 months without splenectomy, but none had hypersplenism. Splenectomy for treatment of poor engraftment after transplantation in patients with hypersplenism has proved beneficial in other disease settings [36,37], but prophylactic splenectomy for patients with myeloproliferative disorders and splenomegaly in the absence of hypersplenism, splenic infarct, or other complications does not seem to be warranted [38].

Our institutional experience and review of the literature support the use of allogeneic transplantation as treatment for poor-prognosis chronic myeloproliferative disorders. Follow-up information for these patients is limited, and published literature may be biased for cases with good outcome, but the overall survival rate in this series is similar to that of patients transplanted for chronic myelogenous leukemia in accelerated phase [39]. It should be noted, however, that none of the patients reported here had more than 30% blasts at the time of transplantation. Whether allogeneic transplantation would benefit patients with chronic myeloproliferative disorders in overt blast transformation remains to be determined.

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